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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,610	11/08/2001	Patrick Aebischer	674523-2013	2486

20999 7590 08/26/2003

FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,610	AEBISCHER ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11/8/01 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The filing date for the provisional application 60/247,604 on the Declaration is erroneously listed as November 9, 2001 rather than the correct date of November 9, 2000.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim methods of treating or preventing neurological diseases such as PD by administering a lentiviral vector encoding any GDNF, a variant, homolog, analog or derivative of human GDNF that has the activity of GDNF. Applicants disclose only the human GDNF coding sequence. The claims read on treatment methods using any

member of a genus of sequences encoding any GDNF or variants, homologs, analogs or derivatives of the human GDNF.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, applicants disclose only the human GDNF coding sequence and present no correlation between the structure of the one disclosed species and the biological functions of the GDNF molecule. Applicants present no description of the functional motifs of the human GDNF molecule which would need to be present (or conserved) for biological activities in any GDNF derived from any other species, or in any homolog, analog or derivative of human GDNF. The skilled artisan would therefore be unable to envision the structures of the recited GDNF analogs, homologs and derivatives with each having to be determined empirically. Since the claims read broadly on any GDNF or any variant, derivative or analog of human GDNF and since neither applicants nor the prior art have not provided a correlation between the structure of the one disclosed species and the biological functions of GDNF, it must be considered that the single disclosed species is not a representative number of species sufficient for the skilled artisan to conclude that applicants were in possession of the claimed genus.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim gene therapy protocols for the treatment or prevention (in any mammal) of any neurodegenerative disease or specifically, Parkinson's Disease (PD), wherein said treatment involves administering recombinant lentiviral vectors encoding a growth factor (specifically GDNF) to the nervous system or specifically, the brain.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) Unpredictability of the art. The gene therapy art is extremely unpredictable. The unpredictability is manifested in the poor and unpredictable delivery of vectors to the target cells or tissues in vivo, the transient and unpredictable expression of transgenes in cells in vivo and the difficulty in extrapolating the results of animal studies to humans (See Anderson, Nature, 1998, Vol. 392, pp. 25-30; Verma et al., Nature, 1997, Vol. 389,

pp. 239-242; Kmeic, American Scientist, 1999, Vol. 87, pp. 240-247; Fox, Nature Biotechnology, 2000, Vol. 18, pp. 143-144; Mountain, TIBTECH, 2000, Vol. 18, pp. 119-128, etc. for reviews of the well known unpredictability associated with gene therapy protocols). With regard to use of retroviral vectors for gene therapy, specific problems (as a result of integration of the vector nucleic acid into the chromosomal DNA) encountered in vivo include transgene (promoter) "silencing" which likely results from methylation in the vicinity of the promoter and the induction of cancers in patients treated with retroviral gene therapy vectors (See Marshall, Science, Vol. 299, 2003, p. 320). Indeed, Marshall notes that as of Feb. 2003. all retroviral based gene therapy clinical studies were suspended in the U.S. pending a safety review. It is unclear how the skilled artisan would use the recited lentiviral vectors to treat or prevent neurodegenerative diseases when the treatment itself could result in development of cancers in the patients so treated. Specifically, with regard to use of lentiviral gene therapy vectors to **prevent** neurodegenerative diseases, said prevention would require long term (possibly life-long) expression of the growth factor transgene. Given that one of the main obstacles to gene therapy is the short term, transient and unpredictable expression of transgenes in cells in vivo, it must be considered that use of lentiviral gene therapy vectors for prevention of neurodegenerative disease is totally unpredictable and would require significant new scientific break-throughs in the gene therapy art and in the art regarding the molecular biology and physiology of neurodegenerative diseases to be even contemplated.

Specifically, with regard to use of lentiviral gene therapy vectors for treatment of PD, the unpredictability in the art is exemplified by Kordower et al. (Science, 2000, Vol. 290, pp. 767-773). Kordower et al. (including one of the applicants on the instant application) demonstrate use of a lentiviral vector to deliver GNDF to the striatum and substantia nigra of aged rhesus monkeys and monkeys previously treated with MPTP. The results show prevention of nigrostriatal degeneration and possible cellular regeneration in these primates. This data is essentially the same as disclosed in the instant application. However, with regard to use of lentiviral vectors to treat or prevent PD, Kordower et al. notes that:

> We injected lentivirus into both the striatum and substantia nigra in order to maximize the chance for an effect. For lenti-GDNF therapy to be a practical clinical approach, studies determining the regions of GDNF delivery critical to reverse progressive nigrostriatal degeneration are needed. The importance of related biological events such as anterograde transport of GDNF from injection regions also needs to be established. Finally, potential adverse events resulting from lenti-GDNF inducing supranormal levels of striatal dopamine needs to be evaluated. Toward this end, vectors with built-in inducible systems that can modulate gene expression in cases of dose-limiting side effects need to be developed. (Kordower et al., p. 772).

Clearly, Kordower et al. indicates that significant further research is required before lentiviral vectors can be used in any clinical protocols for treatment of PD.

Finally, it is noted that similar unpredictability exists with regard to gene therapy treatments of other neurodegenerative diseases such as Alzheimer's Disease, frontal lobe dementia (Pick's Disease), progressive supranuclear palsy (PSP), ALS, Huntington's Disease, multiple sclerosis, etc. It is unclear if any suitable animal models of these diseases exist and applicants have provided no data on this. Applicants present no guidance on what growth factors would need to be expressed to treat, for

example, Alzheimer's Disease or PSP, no guidance is provided on what specific target cells would need to be infected by the lentiviral vectors to treat any given (non-PD) neurodegenerative disease, no guidance is provided on how the skilled artisan would overcome the art recognized hurdles to successful gene therapy, etc.

2) State of the art. The state of the art at the time of applicants' invention was poorly developed (actually nil) with no unambiguous demonstration of a success in any gene therapy treatment (or prevention) of a human neurodegenerative disease.

3) Number of working example. Applicants present no working examples of treatment or prevention of any neurodegenerative disease in humans or any mammal.

4) Amount of guidance presented. Applicants provide data using primate models of PD. This data is essentially the same as that disclosed in the Kordower et al. reference (cited above). Applicants however, present no disclosure of an art recognized correlation between the results obtained in the recited primate models and the results the skilled artisan would expect to obtain in treatment of humans with PD. Without an art recognized nexus between the results obtained in the animal models and the results which the skilled artisan would expect to obtain in humans, the animal model data is impossible to interpret and is not sufficient to enable the claimed invention. No guidance is presented on the treatment of any other specific neurodegenerative disease in humans or any other mammal.

5) Scope of the invention. The broadest claims encompass treatment or prevention of any neurodegenerative disease in any mammal using any lentiviral vector encoding any growth factor. These claims must be considered very broad.

6) Nature of the invention. The nature of the invention involves one of the most complex areas of molecular biology/medicine, treatment of neurodegenerative diseases using gene therapy vectors.

7) Level of skill in the art. The level of skill in the art is very low. While the credentials of practitioners in the gene therapy art can be impressive (Ph.D.s and M.D.s) , the level of skill in **actually practicing gene therapy is very low** because those of skill in the art have been unable to successfully reduce to practice gene therapy for treatment or prevention of any neurodegenerative disease.

Given the analysis of the above factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have needed to have practiced undue and excessive experimentation in order to practice the claimed invention.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (703) 305-1998. The fax phone

number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
August 24, 2003

DAVID GUZO
PRIMARY EXAMINER